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(71) Applicant (for all designated States except US): CELL-
TECH CHIROSCIENCE LIMITED [GB/GB]; 216 Bath
Road, Slough, Berkshire SL1 4EN (GB).

(72) Inventors; and

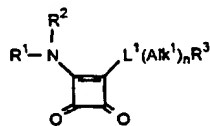
(75) Inventors/Applicants (for US only): LANGHAM, Barry,
John [GB/GB]; 166 Kingfisher Drive, Woodley, Reading,
Berkshire RG5 3LQ (GB). ALEXANDER, Rikki, Peter
[GB/GB]; 14 Carrington Road, High Wycombe, Buck-
inghamshire HP12 3HY (GB). HEAD, John, Clifford
[GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire
SL6 6RX (GB). LINSLEY, Janeen, Marsha [GB/GB];
290 Hughenden Road, High Wycombe, Buckingham
HP13 5PE (GB). PORTER, John, Robert [GB/GB];5 Farm Place, Henton, Chinnor, Oxfordshire OX9 4AD
(GB). ARCHIBALD, Sarah, Catherine [GB/GB]; 5
College Glen, Maidenhead, Berkshire SL6 6BL (GB).
WARRELOW, Graham, John [GB/GB]; Oakside, 4
Wieland Road, Northwood, Middlesex HA6 3QU (GB).(74) Agents: MERCER, Christopher, Paul et al.; Carpmaels
& Ransford, 43 Bloomsbury Square, London WC1A 2RA
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(54) Title: SQUARIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS



(1)

-CH₂-CH(R)-

-CH=C(R)-



(a)

WO 01/47867 A1

(57) Abstract: Squaric acid derivatives of formula (1) are described wherein R¹ is a group Ar¹ Ar²Alk- in which Ar¹ is an option-
ally substituted aromatic or heteroaromatic group; Ar² is an optionally substituted phenylene or nitrogen-containing six-membered
heteroarylene group; and Alk is a chain -CH₂-CH(R)-, CH=C(R)-, (a) in which R is a carboxylic acid (-CO₂H) or a derivative
or biostere thereof; R² is a hydrogen atom or a C₁₋₆alkyl group; L¹ is a covalent bond or a linker atom or group; n is zero or the
integer 1; Alk¹ is an optionally substituted aliphatic chain; R³ is a hydrogen atom or an optionally substituted heteroaliphatic, cy-
cloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group; and the salts,
solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of integrins to their ligands and are of use in
the prophylaxis and treatment of immune or inflammatory disorders, or disorders involving the inappropriate growth or migration
of cells.

SQUARIC ACID DERIVATIVES AS INTEGRIN ANTAGONISTS

This invention relates to a series of biaryl squaric acid derivatives, to
5 compositions containing them, to processes for their preparation, and to
their use in medicine.

Over the last few years it has become increasingly clear that the physical
interaction of inflammatory leukocytes with each other and other cells of
10 the body plays an important role in regulating immune and inflammatory
responses [Springer, T. A., Nature, 346, 425, (1990); Springer, T. A., Cell,
76, 301, (1994)]. Specific cell surface molecules collectively referred to as
cell adhesion molecules mediate many of these interactions.

15 The adhesion molecules have been sub-divided into different groups on
the basis of their structure. One family of adhesion molecules which is
believed to play a particularly important role in regulating immune and
inflammatory responses is the integrin family. This family of cell surface
glycoproteins has a typical non-covalently linked heterodimer structure. At
20 least 16 different integrin alpha chains and 8 different integrin beta chains
have been identified [Newman, P. et al, Molecular Medicine Today, 304,
(1996)]. The members of the family are typically named according to their
heterodimer composition although trivial nomenclature is widespread in the
field. Thus the integrin $\alpha 4\beta 1$ consists of the integrin alpha 4 chain
25 associated with the integrin beta 1 chain, but is also widely referred to as
Very Late Antigen 4 or VLA-4. Not all of the potential pairings of integrin
alpha and beta chains have yet been observed in nature and the integrin
family has been subdivided into a number of subgroups based on the
pairings that have been recognised to date [Sonnenberg, A., Current
30 Topics in Microbiology and Immunology, 184, 7, (1993)].

The importance of integrin function in normal physiological responses is
highlighted by two human deficiency diseases in which integrin function is
defective. Thus in the disease termed Leukocyte Adhesion Deficiency
35 (LAD) there is a defect in one of the families of integrins expressed on
leukocytes [Marlin, S. D. et al, J. Exp. Med. 164, 855, (1986)]. Patients

suffering from this disease have a reduced ability to recruit leukocytes to inflammatory sites and suffer recurrent infections, which in extreme cases may be fatal. In the case of patients suffering from the disease termed Glanzman's thrombasthenia (a defect in a member of the beta 3 integrin family) there is a defect in blood clotting (Hodivala-Dilke, K. M., J. Clin. Invest. 103, 229, (1999)).

The potential to modify integrin function in such a way as to beneficially modulate cell adhesion has been extensively investigated in animal models using specific antibodies and peptides that block various functions of these molecules [e.g. Issekutz, T. B., J. Immunol. 149, 3394, (1992); Li, Z. *et al*, Am. J. Physiol. 263, L723, (1992); Mitjans, F. *et al*, J. Cell Sci. 108, 2825, (1995); Brooks, P. C. *et al*, J. Clin. Invest. 96, 1815, (1995); Binns, R. M. *et al*, J. Immunol. 157, 4094, (1996); Hammes, H.-P. *et al*, Nature Medicine 2, 529, (1996); Srivata, S. *et al*, Cardiovascular Res. 36, 408 (1997)]. A number of monoclonal antibodies which block integrin function are currently being investigated for their therapeutic potential in human disease, and one, ReoPro, a chimeric antibody against the platelet integrin α IIb β 3 is in use as a potent anti-thrombotic agent for use in patients with cardiovascular complications following coronary angioplasty.

Integrins recognize both cell surface and extracellular matrix ligands, and ligand specificity is determined by the particular alpha-beta subunit combination of the molecule [Newman, P., *ibid*]. One particular integrin subgroup of interest involves the α 4 chain which can pair with two different beta chains β 1 and β 7 [Sonnenberg, A., *ibid*]. The α 4 β 1 pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes, eosinophils and basophils) although it is absent or only present at low levels on circulating neutrophils. α 4 β 1 binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L., Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*, Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between α 4 β 1 and ligands on other cells and the extracellular matrix plays

an important role in leukocyte migration and activation [Yednock, T. A. *et al*, *Nature*, 356, 63, (1992); Podolsky, D. K. *et al*, *J. Clin. Invest.* 92, 372, (1993); Abraham, W. M. *et al*, *J. Clin. Invest.* 93, 776, (1994)].

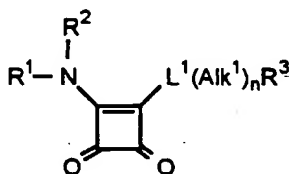
5 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B. and Weissman, I. L., *EMBO J.* 8, 1735, (1989)]. The $\alpha 4\beta 7$ pairing is expressed on certain sub-populations of T and B lymphocytes and on eosinophils [Erle, D. J. *et al*, *J. Immunol.* 153, 517 (1994)]. Like $\alpha 4\beta 1$, $\alpha 4\beta 7$ binds to VCAM-1 and fibronectin. In addition,
10 $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, *Cell*, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important sites of inflammation outside of mucosal tissue [Yang, X.-D. *et al*, *PNAS*, 91, 12604, (1994)].

15 Regions of the peptide sequence recognized by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises
20 a LDT sequence in MAdCAM-1 [Birskin, M. J. *et al*, *J. Immunol.* 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al*, *J. Biol. Chem.*, 269, 18668, (1994); Shorff, H. N. *et al*, *Biorganic Med. Chem. Lett.*, 6, 2495, (1996); Vanderslice, P. *et al*, *J.*
25 *Immunol.*, 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A., *et al*, *PNAS*, 88, 8072, (1991)].

30 Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other memb rs of the integrin family it is important to be able to identify selectiv
35 inhibitors of the alpha 4 subgroup.

We have now found a group of compounds which are potent and selective inhibitors of α_4 integrins. Members of the group are able to inhibit α_4 integrins such as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. These compounds possess the additional advantage of good pharmacokinetic properties, especially low plasma clearance.

Thus according to one aspect of the invention we provide a compound of formula (1)

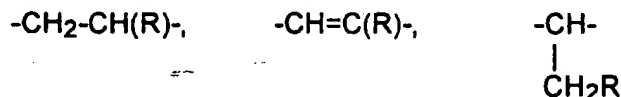


(1)

wherein

R¹ is a group Ar¹Ar²Alk- in which:

- Ar¹ is an optionally substituted aromatic or heteroaromatic group;
 Ar² is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; and Alk is a chain



in which R is a carboxylic acid (-CO₂H) or a derivative or biostere thereof;

R² is a hydrogen atom or a C₁₋₆alkyl group;

L¹ is a covalent bond or a linker atom or group;

- n is zero or the integer 1;

Alk¹ is an optionally substituted aliphatic chain;

R³ is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group;

- and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more chiral centres, and exist as enantiomers or diastereomers. The invention is

to be understood to extend to all such enantiomers, diastereomers and mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise. In addition, compounds of
5 formula (1) may exist as tautomers, for example keto ($\text{CH}_2\text{C}=\text{O}$)-enol ($\text{CH}=\text{CHOH}$) tautomers. Formula (1) and the formulae hereinafter are intended to represent all individual tautomers and mixtures thereof, unless stated otherwise.

10 Optionally substituted aromatic groups represented by Ar^1 when present in the group R^1 include for example optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

15 Optionally substituted heteroaromatic groups represented by the group Ar^1 when present in the group R^1 include for example optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic
20 fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups
25 containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N- C_{1-6} alkylimidazolyl, oxazolyl,
30 isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, isobenzofuryl, [2,3-dihydro]benzofuryl, [2,3-dihydro]benzothienyl, benzothienyl, benzotriazolyl,
35 indolyl, indolynyl, isoindolyl, indazolynyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzoisoxazolyl, benzopyranyl,

[3,4-dihydro]benzopyranyl, benzofurazonyl, quinazolinyl, purinyl, quinoxaliny, naphthyridinyl, especially 2,6-naphthyridinyl, pyrido[3,4-b]pyridyl, phthalazinyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Each aromatic or heteroaromatic group represented by the group Ar¹ may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group -L²(Alk²)_tL³(R⁴)_u in which L² and L³ which may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk² is an aliphatic or heteroaliphatic chain and R⁴ is a hydrogen or halogen atom or a group selected from optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R⁵)- (where R⁵ is a hydrogen atom or an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl group), -C(O)- or -C(S)- groups], -OR⁵ -SR⁵, -NR⁵R⁶ [where R⁶ is as just defined for R⁵ and may be the same or different], -NO₂, -CN, -CO₂R⁵, -SO₃H, -SOR⁵, -SO₂R⁵, -SO₃R⁵, -OCO₂R⁵, -CONR⁵R⁶, -OCONR⁵R⁶, -CSNR⁵R⁶, -COR⁵, -OCOR⁵, -N(R⁵)COR⁶, -N(R⁵)CSR⁶, -SO₂N(R⁵)(R⁶), -N(R⁵)SO₂R⁶, -CON(R⁵)SO₂R⁶, -N(R⁵)CON(R⁶)(R⁷) [where R⁷ is a hydrogen atom or an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl group], -N(R⁵)CSN(R⁶)(R⁷) or -N(R⁵)SO₂N(R⁶)(R⁷), provided that when t is zero and each of L² and L³ is a covalent bond then u is the integer 1 and R⁴ is other than a hydrogen atom

When L² and/or L³ is present in these substituents as a linker atom or group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R⁸)- [where R⁸ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group], -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸)-, or -N(R⁸)SO₂N(R⁸)- groups. Where

the linker group contains two R^8 substituents, these may be the same or different.

When R^4 , R^5 , R^6 , R^7 and/or R^8 is present as a C_{1-6} alkyl group it may be a straight or branched C_{1-6} alkyl group, e.g. a C_{1-4} alkyl group such as a methyl, ethyl, i-propyl or t-butyl group. C_{3-8} cycloalkyl groups represented by R^4 , R^5 , R^6 , R^7 and/or R^8 include C_{3-6} cycloalkyl groups e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. Optional substituents which may be present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, hydroxy or C_{1-6} alkoxy e.g. methoxy or ethoxy groups or optionally substituted C_6-12 aryl or optionally substituted C_{1-9} heteroaryl. Optionally substituted aryl and heteroaryl groups include those groups just described for the group Ar^1 .

When the groups R^5 and R^6 or R^6 and R^7 are both C_{1-6} alkyl groups these groups may be joined, together with the N atom to which they are attached, to form a heterocyclic ring. Such heterocyclic rings may be optionally interrupted by a further heteroatom selected from -O-, -S- or -N(R^5)-. Particular examples of such heterocyclic rings include piperidinyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, imidazolidinyl and piperazinyl rings.

When Alk^2 is present as an aliphatic or heteroaliphatic chain it may be for example any divalent chain corresponding to the below-mentioned aliphatic or heteroaliphatic group described for Alk^1 or R^3 respectively.

Halogen atoms represented by R^4 in the optional Ar^1 substituents include fluorine, chlorine, bromine, or iodine atoms.

Examples of the substituents represented by $-L^2(Alk^2)_tL^3(R^4)_u$ when present in Ar^1 groups in compounds of the invention include atoms or groups $-L^2Alk^2L^3R^4$, $-L^2Alk^2R^4$, $-L^2R^4$ and $-Alk^2R^4$ wherein L^2 , Alk^2 , L^3 and R^4 are as defined above. Particular examples of such substituents include $-L^2CH_2L^3R^4$, $-L^2CH(CH_3)L^3R^4$, $-L^2CH(CH_2)_3L^3R^4$, $-L^2CH_2R^4$,

$-L^2CH(CH_3)R^4$, $-L^2(CH_2)_2R^4$, $-CH_2R^4$, $-CH(CH_3)R^4$, $-(CH_2)_2R^4$ and $-R^4$ groups.

Thus Ar^1 in compounds of the invention may be optionally substituted for
 5 example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C_{1-6} alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C_{3-8} cycloalkyl, e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, C_{1-6} hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or $-C(OH)(CF_3)_2$, pyrrolidinyl, imidazolidinyl, pyrazolidinyl,
 10 piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, oxazolidinyl, carboxy C_{1-6} alkyl, e.g. carboxyethyl, C_{1-6} alkylthio e.g. methylthio or ethylthio, carboxy C_{1-6} alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C_{1-6} alkoxy, e.g. methoxy or ethoxy, hydroxy C_{1-6} alkoxy, e.g. 2-hydroxyethoxy, halo C_{1-6} alkyl, e.g. $-CF_3$, $-CHF_2$, $-CH_2F$,
 15 halo C_{1-6} alkoxy, e.g. $-OCF_3$, $-OCHF_2$, $-OCH_2F$, C_{1-6} alkylamino, e.g. methylamino or ethylamino, amino ($-NH_2$), amino C_{1-6} alkyl, e.g. aminomethyl or aminoethyl, C_{1-6} dialkylamino, e.g. dimethylamino or diethylamino, C_{1-6} alkylamino C_{1-6} alkyl, e.g. ethylaminoethyl, C_{1-6} dialkylamino C_{1-6} alkyl, e.g. diethylaminoethyl, amino C_{1-6} alkylamino e.g.
 20 aminoethylamino, amino C_{1-6} alkoxy, e.g. aminoethoxy, hydroxy C_{1-6} alkylamino e.g. hydroxyethylamino or hydroxypropylamino, C_{1-6} alkylamino C_{1-6} alkoxy, e.g. methylaminoethoxy, C_{1-6} dialkylamino C_{1-6} alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl ($-OH$),
 25 formyl [$HC(O)-$], carboxyl ($-CO_2H$), $-CO_2Alk^3$ [where Alk^3 is as defined below for Alk^7], C_{1-6} alkanoyl e.g. acetyl, thiol ($-SH$), thio C_{1-6} alkyl, e.g. thiomethyl or thioethyl, sulphonyl ($-SO_3H$), $-SO_3Alk^3$, C_{1-6} alkylsulphinyl e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl, C_{1-6} alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl ($-SO_2NH_2$), C_{1-6} alkylamino-
 30 sulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C_{1-6} dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido ($-CONH_2$), C_{1-6} alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C_{1-6} dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, amino C_{1-6} alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C_{1-6} dialkylamino C_{1-6} alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonyl-

amino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, amino-
 5 thiocarbonylamino, C₁₋₆alkylaminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonylamino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, C₁₋₆alkylsulphonylamino, e.g. methyl-
 10 sulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino,
 15 C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino groups.
 20

Where desired, two -L²(Alk²)_tL³(R⁴)_u substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.
 25

Optionally substituted nitrogen-containing six-membered heteroaryl groups represented by Ar² when present as part of the group R¹ include optionally substituted pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl e.g. 1,2,4-triazinyl groups. Each group may be attached to the
 30 remainder of the molecule through any available ring carbon atoms.

The phenylene and nitrogen-containing heteroaryl groups represented by Ar² may be optionally substituted by one or two substituents selected from the atoms or groups -L³(Alk²)_tL³(R⁴)_u described herein. Where two
 35 of these atoms or groups are present they may be the same or different.

When the group R is present in R¹ in compounds of the invention as a derivative of a carboxylic acid it may be for example a carboxylic acid ester or amide. Particular esters and amides include -CO₂Alk⁷ and -CONR⁵R⁶ groups as defined herein. When R is a biostere of a carboxylic acid it may
 5 be for example a tetrazole or other acid such as phosphonic acid, phosphinic acid, sulphonic acid, sulphinic acid or boronic acid or an acylsulphonamide group.

Ester (-CO₂Alk⁷) and amide (-CONR⁵R⁶) derivatives of the carboxylic acid group (-CO₂H) in compounds of formula (1) may advantageously be used
 10 as prodrugs of the active compound. Such prodrugs are compounds which undergo biotransformation to the corresponding carboxylic acid prior to exhibiting their pharmacological effects and the invention particularly extends to prodrugs of the acids of formula (1). Such prodrugs are well
 15 known in the art, see for example International Patent Application No. WO00/23419, Bodor, N. (Alfred Benzon Symposium, 1982, 17, 156-177), Singh, G. et al (J. Sci. Ind. Res., 1996, 55, 497-510) and Bundgaard, H., (Design of Prodrugs, 1985, Elsevier, Amsterdam).

20 Esterified carboxyl groups represented by the group -CO₂Alk⁷ include those wherein Alk⁷ is a straight or branched optionally substituted C₁₋₈alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; an optionally substituted C₂₋₈alkenyl group such as a propenyl e.g. 2-propenyl or butenyl e.g. 2-butenyl or 3-butenyl group, an
 25 optionally substituted C₂₋₈alkynyl group such as a ethynyl, propynyl e.g. 2-propynyl or butynyl e.g. 2-butynyl or 3-butynyl group, an optionally substituted C₃₋₈cycloalkyl group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group; an optionally substituted C₃₋₈cycloalkylC₁₋₈alkyl group such as a cyclopentylmethyl, cyclohexylmethyl
 30 or cyclohexylethyl group; an optionally substituted C₃₋₈heterocycloalkylC₁₋₆alkyl group such as a morpholinyl-N-ethyl, thiomorpholinyl-N-methyl, pyrrolidinyl-N-ethyl, pyrrolidinyl-N-propyl, piperidinyl-N-ethyl, pyrazolidinyl-N-methyl or piperazinyl-N-ethyl group; an optionally substituted C₁₋₆alkyloxyC₁₋₆alkyl group such as a methoxyethyl or propoxyethyl
 35 group; an optionally substituted C₁₋₆alkylthioC₁₋₆alkyl group such as an ethylthioethyl group; an optionally substituted C₁₋₆alkylsulfinylC₁₋₆alkyl

group such as an methylsulfinylethyl group; an optionally substituted C₁₋₆alkylsulfonylC₁₋₆alkyl group such as an methylsulfonylmethyl group; an optionally substituted C₃₋₈cycloalkyloxyC₁₋₆alkyl group such as a cyclohexyloxymethyl group; an optionally substituted C₃₋₈cycloalkylthioC₁₋₆alkyl group such as a cyclopentylthiomethyl group; an optionally substituted C₃₋₈cycloalkylsulfinylC₁₋₆alkyl group such as a cyclopentylsulfinylmethyl group; an optionally substituted C₃₋₈cycloalkylsulfonylC₁₋₆alkyl group such as a cyclopentylsulfonylmethyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkyl group such as isobutoxycarbonylpropyl group; an optionally substituted C₁₋₆alkyloxycarbonylC₁₋₆alkenyl group such as isobutoxycarbonylpentenyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkyl group such as an isopropoxycarbonyloxyethyl e.g. a 1-(isopropoxycarbonyloxy)-ethyl, 2-(isopropoxycarbonyloxy)ethyl or ethyloxycarbonyloxymethyl group; an optionally substituted C₁₋₆alkyloxycarbonyloxyC₁₋₆alkenyl group such as a isopropoxycarbonyloxybutenyl group, an optionally substituted C₃₋₈cycloalkyloxycarbonyloxyC₁₋₆alkyl group such as a cyclohexyloxycarbonyloxyethyl, e.g. a 2-(cyclohexyloxycarbonyloxy)ethyl group, an optionally substituted N-di-C₁₋₈alkylaminoC₁₋₈alkyl group such as a N-dimethylaminoethyl or N-diethylaminoethyl group; an optionally substituted N-C₆₋₁₂aryl-N-C₁₋₆alkylaminoC₁₋₆alkyl group such as a N-phenyl-N-methylaminomethyl group; an optionally substituted N-di-C₁₋₈alkylcarbamoylC₁₋₈alkyl group such as a N-diethylcarbamoylmethyl group; an optionally substituted C₆₋₁₀arylC₁₋₆alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C₆₋₁₀aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C₆₋₁₀aryloxyC₁₋₈alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; a C₆₋₁₂arylthioC₁₋₈alkyl group such as an optionally substituted phenylthioethyl group; a C₆₋₁₂arylsulfinylC₁₋₈alkyl group such as an optionally substituted phenylsulfinylmethyl group; a C₆₋₁₂arylsulfonylC₁₋₈alkyl group such as an optionally substituted phenylsulfonylmethyl group; an optionally substituted C₁₋₈alkanoyloxyC₁₋₈alkyl group, such as a ac toxymethyl, ethoxycarbonyloxyethyl, pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; an optionally substituted C₄₋₈imidoC₁₋₈alkyl

group such as a succinimidomethyl or phthalamidoethyl group; a C₆-
12-aryloxyC₁₋₈alkyl group such as an optionally substituted benzoyloxy-
ethyl or benzoyloxypropyl group or a triglyceride such as a 2-substituted
triglyceride e.g. a 1,3-di-C₁₋₈alkylglycerol-2-yl group such as a 1,3-
5 diheptylglycerol-2-yl group. Optional substituents present on the Alk⁷
group include R^{13a} substituents described above.

It will be appreciated that in the forgoing list of Alk⁷ groups the point of
attachment to the remainder of the compound of formula (1) is via the last
10 described part of the Alk⁷ group. Thus, for example a methoxyethyl group
would be attached by the ethyl group, whilst a morpholinyl-N-ethyl group
would be attached via the N-ethyl group.

It will be further appreciated that in the forgoing list of Alk⁷ groups, where
15 not specifically mentioned, alkyl groups may be replaced by alkenyl or
alkynyl groups where such groups are as previously defined for Alk¹.
Additionally these alkyl, alkenyl or alkynyl groups may optionally be
interrupted by one, two or three linker atoms or groups where such linker
atoms and groups are as previously defined for L².

20 When the group R² is present in compounds of the invention as a C₁₋₆alkyl
group it may be for example a straight or branched C₁₋₆alkyl group, e.g. a
C₁₋₄alkyl group such as a methyl or ethyl group.

25 The linker atom or group represented by L¹ in compounds of formula (1)
may be any linker atom or group as described above for the linker atom or
group L² or may represent a covalent bond.

When the group Alk¹ is present in compounds of formula (1) as an
30 optionally substituted aliphatic chain it may be an optionally substituted C₁-
10 aliphatic chain. Particular examples include optionally substituted
straight or branched chain C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆
alkynylene chains.

35 Particular examples of aliphatic chains represented by Alk¹ include
optionally substituted -CH₂-, -(CH₂)₂-, -CH(CH₃)CH₂-, -(CH₂)₂CH₂-,

- $-(CH_2)_3CH_2-$, $-CH(CH_3)(CH_2)_2-$, $-CH_2CH(CH_3)CH_2-$, $-C(CH_3)_2CH_2-$,
 $-CH_2C(CH_3)_2CH_2-$, $-(CH_2)_2CH(CH_3)CH_2-$, $-CH(CH_3)(CH_2)_3-$,
 $-CH(CH_3)CH_2CH(CH_3)CH_2-$, $-CH_2CH(CH_3)CH_2CH_2-$,
 $-(CH_2)_2C(CH_3)_2CH_2-$, $-(CH_2)_4CH_2-$, $-(CH_2)_5CH_2-$, $-CHCH-$, $-CHCHCH_2-$,
 5 $-CH_2CHCH-$, $-CHCHCH_2CH_2-$, $-CH_2CHCHCH_2-$, $-(CH_2)_2CHCH-$, $-CC-$,
 $-CCCH_2-$, $-CH_2CC-$, $-CCCH_2CH_2-$, $-CH_2CCCH_2-$ or $-(CH_2)_2CCH-$ groups.

Heteroaliphatic groups represented by the group R^3 in the compounds of formula (1) include the aliphatic chains just described for Alk^1 but with each containing a terminal hydrogen atom and additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L^4 where L^4 is as defined above for L^2 when L^2 is a linker atom or group. Each L^4 atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group. Particular examples include optionally substituted $-L^4CH_3$, $-CH_2L^4CH_3$, $-L^4CH_2CH_3$, $-CH_2L^4CH_2CH_3$, $-(CH_2)_2L^4CH_3$, $-(CH_2)_3L^4CH_3$, $-L^4(CH_2)_2CH_3$ and $-(CH_2)_2L^4CH_2CH_3$ groups.

- 20 The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 and R^3 respectively include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or $-OH$, $-CN$, $-CO_2H$, $-CO_2R^9$ [where R^9
 25 is an optionally substituted straight or branched C_{1-6} alkyl group as defined above for R^4], $-CONHR^9$, $-CON(R^9)_2$, $-COR^9$, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, $-S(O)R^9$, $-S(O)_2R^9$, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups or optionally substituted C_{6-12} aryl e.g. phenyl or C_{1-9} heteroaryl e.g. pyridyl. Substituted amino groups include
 30 $-NHR^9$ and $-N(R^9)_2$ groups. Where two R^9 groups are present in any of the above substituents these may be the same or different.

Optionally substituted cycloaliphatic groups represented by the group R^3 in compounds of the invention include optionally substituted C_{3-10} cycloaliphatic groups. Particular examples include optionally substituted
 35

C₃₋₁₀ cycloalkyl, e.g. C₃₋₇ cycloalkyl or C₃₋₁₀ cycloalkenyl, e.g. C₃₋₇ cycloalkenyl groups.

5 Optionally substituted heterocycloaliphatic groups represented by the group R³ include optionally substituted C₃₋₁₀ heterocycloaliphatic groups. Particular examples include optionally substituted C₃₋₁₀ heterocycloalkyl, e.g. C₃₋₇ heterocycloalkyl, or C₃₋₁₀ heterocycloalkenyl, e.g. C₃₋₇ heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L⁴ as defined above.

10 Optionally substituted polycycloaliphatic groups represented by the group R³ include optionally substituted C₇₋₁₀ bi- or tricycloalkyl or C₇₋₁₀ bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R³ include the optionally substituted
15 polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L⁴ atoms or groups.

Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group R³
20 include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-
25 imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranal, e.g. 2- or 4-pyranal, piperidinyl, homopiperidinyl, heptamethyleneiminyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, thiomorpholinyl, piperazinyl, homopiperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-,
30 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups
35 represented by the group R³ include one, two, three or more substituents

each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF₃)₂, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, -C₁₋₆alkoxyC₁₋₆alkyl e.g. methoxyethyl-, C₁₋₆alkylthio e.g. methylthio or ethylthio, or -(Alk⁴)_vR¹⁰ groups in which Alk⁴ is a straight or branched C₁₋₃alkylene chain, v is zero or an integer 1 and R¹⁰ is a -OH, -SH, -N(R¹¹)₂ (in which R¹¹ is an atom or group as defined herein for R⁸) -CN, -CO₂R¹¹, -NO₂, -CON(R¹¹)₂, -CSN(R¹¹)₂, -COR¹¹, -CSN(R¹¹)₂, -N(R¹¹)COR¹¹, -N(R¹¹)CSR¹¹, -SO₂N(R¹¹)₂, -N(R¹¹)SO₂R¹¹, -N(R¹¹)CON(R¹¹)₂, -N(R¹¹)CSN(R¹¹), N(R¹¹)SO₂N(R¹¹)₂, -SOR¹¹, -SO₂R¹¹, -SO₃R¹¹ or an optionally substituted aromatic or heteroaromatic group. Where two R¹¹ atoms or groups are present in these substituents these may be the same or different.

Particular examples of Alk⁴ chains include -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂- and -CH(CH₃)CH₂- chains.

20

Additionally, when the group R³ is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group -(L⁵)_p(Alk⁵)_qR¹² in which L⁵ is -C(O)-, -C(O)O-, -C(S)-, -S(O)₂-, -CON(R¹¹)-, -CSN(R¹¹)- or SO₂N(R¹¹)-, p is zero or an integer 1; Alk⁵ is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or the integer 1; and R¹² is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group.

30 Optionally substituted aliphatic or heteroaliphatic chains represented by Alk⁵ include those optionally substituted chains described above for Alk¹ and R³ respectively.

35 Cycloaliphatic, heterocycloaliphatic, polycycloaliphatic or polyheterocycloaliphatic groups represented by R¹² include those groups just described for the group R³. Optional substituents which may be present on these

groups include those described above in relation to Alk^1 and R^3 aliphatic and heteroaliphatic chains.

5 Aromatic and heteroaromatic groups represented by R^{10} and R^{12} include those groups described hereinbefore for the group Ar^1 . Optional substituents which may be present on these groups include those described in relation to R^3 aromatic and heteroaromatic groups.

10 When the group R^3 is an optionally substituted aromatic or heteroaromatic group it may be for example an aromatic or heteroaromatic group as described herein for the group Ar^1 .

Optional substituents which may be present on the aromatic or heteroaromatic groups represented by the group R^3 include one, two, 15 three or more substituents, each selected from an atom or group R^{13} in which R^{13} is $-\text{R}^{13a}$ or $-\text{Alk}^6(\text{R}^{13a})_m$, where R^{13a} is a halogen atom, or an amino ($-\text{NH}_2$), substituted amino, nitro, cyano, amidino, hydroxyl ($-\text{OH}$), substituted hydroxyl, formyl, carboxyl ($-\text{CO}_2\text{H}$), esterified carboxyl, thiol ($-\text{SH}$), substituted thiol, $-\text{COR}^{14}$ [where R^{14} is an $-\text{Alk}^6(\text{R}^{13a})_m$, aryl or heteroaryl group], $-\text{CSR}^{14}$, $-\text{SO}_3\text{H}$, $-\text{SOR}^{14}$, $-\text{SO}_2\text{R}^{14}$, $-\text{SO}_3\text{R}^{14}$, $-\text{SO}_2\text{NH}_2$, 20 $-\text{SO}_2\text{NHR}^{14}$, $\text{SO}_2\text{N}(\text{R}^{14})_2$, $-\text{CONH}_2$, $-\text{CSNH}_2$, $-\text{CONHR}^{14}$, $-\text{CSNHR}^{14}$, $-\text{CON}(\text{R}^{14})_2$, $-\text{CSN}(\text{R}^{14})_2$, $-\text{N}(\text{R}^{11})\text{SO}_2\text{R}^{14}$, $-\text{N}(\text{SO}_2\text{R}^{14})_2$, $-\text{NH}(\text{R}^{11})\text{SO}_2\text{NH}_2$, $-\text{N}(\text{R}^{11})\text{SO}_2\text{NHR}^{14}$, $-\text{N}(\text{R}^{11})\text{SO}_2\text{N}(\text{R}^{14})_2$, $-\text{N}(\text{R}^{11})\text{COR}^{14}$, $-\text{N}(\text{R}^{11})\text{CONH}_2$, $-\text{N}(\text{R}^{11})\text{CONHR}^{14}$, $-\text{N}(\text{R}^{11})\text{CON}(\text{R}^{14})_2$, 25 $-\text{N}(\text{R}^{11})\text{CSNH}_2$, $-\text{N}(\text{R}^{11})\text{CSNHR}^{14}$, $-\text{N}(\text{R}^{11})\text{CSN}(\text{R}^{14})_2$, $-\text{N}(\text{R}^{11})\text{CSR}^{14}$, $-\text{N}(\text{R}^{11})\text{C}(\text{O})\text{OR}^{14}$, $-\text{SO}_2\text{NHet}^1$ [where NHet^1 is an optionally substituted C_{5-7} cyclicamino group optionally containing one or more other $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^{11})-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{S})-$, $\text{S}(\text{O})$ or $-\text{S}(\text{O})_2$ groups], $-\text{CONHet}^1$, $-\text{CSNHet}^1$, $-\text{N}(\text{R}^{11})\text{SO}_2\text{NHet}^1$, $-\text{N}(\text{R}^{11})\text{CONHet}^1$, $-\text{N}(\text{R}^{11})\text{CSNHet}^1$, 30 $-\text{SO}_2\text{N}(\text{R}^{11})\text{Het}^2$ [where Het^2 is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{N}(\text{R}^{11})-$, $-\text{C}(\text{O})-$ or $-\text{C}(\text{S})-$ groups], $-\text{Het}^2$, $-\text{CON}(\text{R}^{11})\text{Het}^2$, $-\text{CSN}(\text{R}^{11})\text{Het}^2$, $-\text{N}(\text{R}^{11})\text{CON}(\text{R}^{11})\text{Het}^2$, $-\text{N}(\text{R}^{11})\text{CSN}(\text{R}^{11})\text{Het}^2$, cycloaliphatic, heterocycloaliphatic, aryl or heteroaryl group; Alk^6 is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three $-\text{O}-$ or $-\text{S}-$ atoms or $-\text{S}(\text{O})_n$ [where n is an integer 1 or 35

2] or -N(R¹⁵)- groups [where R¹⁵ is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R¹¹ or R¹⁴ groups are present in one of the above substituents, the R¹¹ or R¹⁴ groups may be the same or different.

5

When in the group -Alk⁶(R^{13a})_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in -Alk⁶. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk⁶. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk⁶ becomes an alkyl, alkenyl or alkynyl group.

10

When R^{13a} is a substituted amino group it may be for example a group -NHR¹⁴ [where R¹⁴ is as defined above] or a group -N(R¹⁴)₂ wherein each R¹⁴ group is the same or different.

15

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

20

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group -OR¹⁴ or a -SR¹⁴ or -SC(=NH)NH₂ group respectively.

25

Esterified carboxyl groups represented by the group R^{13a} include groups of formula -CO₂Alk⁷ wherein Alk⁷ is a group as defined hereinbefore.

30

When Alk⁶ is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butyneylene or 3-butyneylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹⁵)- groups.

35

Cycloaliphatic or heterocycloaliphatic groups represented by the groups R^{13a} or R¹⁴ include those optionally substituted C₃₋₁₀cycloaliphatic or C₃₋₁₀ heterocycloaliphatic groups described above for R³.

Aryl or heteroaryl groups represented by the groups R^{13a} or R¹⁴ include mono- or bicyclic optionally substituted C₆₋₁₂ aromatic or C₁₋₉ heteroaromatic groups as described above for the group Ar¹. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

When -NHet¹ or -Het² forms part of a substituent R¹³ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, imidazolidinyl, morpholinyl, thiomorpholinyl, piperidinyl, oxazolidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those substituents described above in relation to R³ heterocycloaliphatic groups.

Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, dioxolanyl, dioxanyl, piperidinyl, oxazolidinyl, thiazolidinyl or imidazolidinyl, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₄₋₇cycloalkyl, e.g. cyclobutyl, cyclopentyl, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino or propylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, aminoC₁₋₆alkylamino e.g. aminoethylamino or aminopropylamino, optionally substituted Het¹NC₁₋₆alkylamino e.g. morpholinopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkyl-aminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋

- alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino, e.g. hydroxyethylamino, hydroxypropylamino, or hydroxybutylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H),
- 5 -CO₂Alk⁷ [where Alk⁷ is as defined above], C₁₋₆ alkanoyl e.g. acetyl, propyl or butyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), -SO₃Alk⁷, C₁₋₆alkylsulphinyl, e.g. methylsulphinyl, ethylsulphinyl or propylsulphinyl,
- 10 C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, ethylsulphonyl, or propylsulphonyl, optionally substituted C₆₋₁₀arylaminosulphonyl, e.g. phenylsulphonyl or dichlorophenylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl, ethylaminosulphonyl or propylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylamino-
- 15 sulphonyl or diethylaminosulphonyl, optionally substituted phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl, ethylaminocarbonyl or propylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆alkyl-
- 20 aminoC₁₋₆alkylaminocarbonyl, e.g. methylaminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino,
- 25 C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonylamino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonylamino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonylamino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonylamino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino,
- 30 e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, haloC₁₋₆alkylsulphonylamino, e.g. trifluoromethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino
- 35 (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, .g.

dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkylamino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, 5 C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, benzylamino, pyridylmethoxy, thiazolyl- 10 methoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

Where desired, two R¹³ substituents may be linked together to form a 15 cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

It will be appreciated that where two or more R¹³ substituents are present, these need not necessarily be the same atoms and/or groups. In general, 20 the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R³.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include 25 pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, 30 alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

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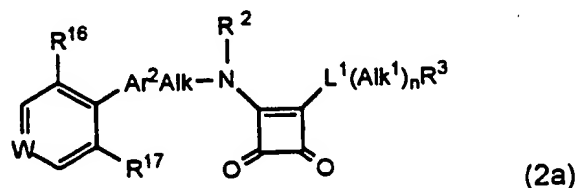
Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

- 10 In the compounds according to the invention the group R^1 is preferably an Ar^1Ar^2Alk - group in which Ar^1 is an optionally substituted phenyl, monocyclic heteroaromatic or bicyclic heteroaromatic group. Particularly useful monocyclic heteroaromatic groups are optionally substituted five- or
- 15 five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on these Ar^1 groups include halogen atoms or alkyl, haloalkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$,
- 20 $-CO_2R^5$, $-NO_2$, $-SOR^5$, $-SO_2R^5$, $-N(R^5)SO_2R^6$, $-SO_2N(R^5)(R^6)$, $-N(R^5)COR^6$, $-N(R^5)CON(R^6)(R^7)$, $-CONR^5R^6$, $-CON(R^5)SO_2R^6$ or $-CN$ groups as described above in relation to the compounds of formula (1). Particularly useful bicyclic heteroaromatic groups represented by Ar^1 include optionally substituted ten-membered fused-ring heteroaromatic
- 25 groups containing one or two heteroatoms, especially nitrogen atoms. Particular examples include optionally substituted naphthyridinyl, especially 2,6-naphthyridinyl, quinolinyl and isoquinolinyl, especially isoquinolin-1-yl groups. Particular optional substituents include those just described for monocyclic heteroaromatic groups.

30

A particularly useful group of compounds according to the invention has the formula (2a):

22



wherein $-W-$ is $-CH=$ or $-N=$;

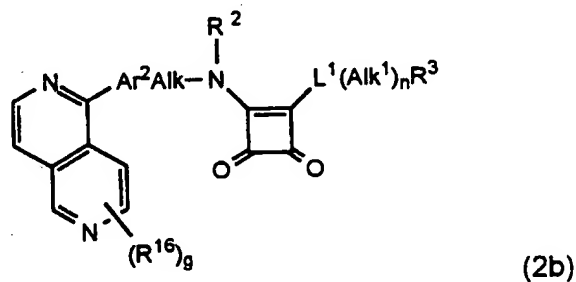
R^{16} and R^{17} , which may be the same or different is each a hydrogen atom or an atom or group $-L^2(Alk^2)_tL^3(R^4)_u$ in which L^2 , Alk^2 , t , L^3 , R^4 and u are as defined previously;

L^1 , Ar^2 , Alk , R^2 , Alk^1 , n and R^3 are as defined for formula (1);

and the salts, solvates, hydrates and N-oxides thereof.

- 10 R^{16} and R^{17} in compounds of formula (2a) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R^{16} and R^{17} substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially $-CF_3$, $-CHF_2$ or $-CH_2F$, methoxy or halomethoxy,
- 15 especially $-OCF_3$, $-OCHF_2$ or $-OCH_2F$ groups.

A further particularly useful group of compounds according to the invention has the formula (2b):



20

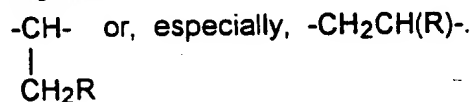
wherein R^{16} , L^1 , Ar^2 , Alk , R^2 , Alk^1 , n and R^3 are as defined for formula (2a);

g is the integer 1, 2, 3 or 4;

- 25 and the salts, solvates, hydrates and N-oxides thereof.

Each R^{16} atom or group in compounds of formula (2b) may be independently selected from an atom or group $-L^2(Alk^3)_tL^3(R^7)_u$ in which L^2 , Alk^2 , t , L^3 , R^4 and u are as previously defined. Particularly useful R^{16} substituents when present in compounds of formula (2b) include halogen atoms, especially fluorine, chlorine or bromine atoms, or methyl, halomethyl, especially $-CF_3$, methoxy or halomethoxy, especially $-OCF_3$, $-CN$, $-CO_2CH_3$, $-NO_2$, amino ($-NH_2$), substituted amino ($-NR^5R^6$) and $-N(R^5)COCH_3$, especially $-NHCOCH_3$ groups.

10 In general Alk in compounds of the invention is preferably:



15 In general in compounds of formulae (1), (2a) and (2b) R^2 is preferably a hydrogen atom.

In one preferred group of compounds of formulae (1), (2a) and (2b) R is a $-CO_2H$ group.

20

In another preferred group of compounds of formulae (1), (2a) and (2b) R is an esterified carboxyl group of formula $-CO_2Alk^7$. In this group of compounds Alk^7 is preferably an optionally substituted C_{1-8} alkyl group, especially a methyl, ethyl, propyl or i-propyl group, a C_{6-10} aryl group, especially a phenyl group, an optionally substituted $C_{6-10}arylC_{1-6}alkyl$ group, especially a benzyl group, a $C_{3-8}heterocycloalkylC_{1-6}alkyl$ group, especially a morpholinyl-N-ethyl group or a $C_{1-6}alkyloxyC_{1-6}alkyl$ group, especially a methoxyethyl group. Especially preferred esterified carboxyl groups include $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CO_2CH_2CH_2CH_3$ and $-CO_2CH(CH_3)_2$ groups.

30

The group Ar^2 in compounds of formulae (1), (2a) and (2b) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

35

In general in compounds of formulae (1), (2a) and (2b) when n is zero or the integer 1 the group R^3 may especially be a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful groups of this type include optionally substituted C_{2-6} heteroalkyl, particularly C_{1-3} alkoxy C_{1-3} alkyl, especially methoxypropyl, optionally substituted C_{3-7} cycloalkyl, especially optionally substituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, optionally substituted C_{5-7} heterocycloaliphatic, especially optionally substituted pyrrolidinyl, thiazolidinyl, pyrrolidinonyl, piperidinyl, morpholinyl or piperazinyl, optionally substituted C_{6-12} aromatic especially optionally substituted phenyl and optionally substituted C_{5-7} heteroaromatic, especially optionally substituted pyridyl, triazinyl or imidazolyl groups. Optional substituents on these groups include in particular R^{13} atoms or groups where R^3 is an aromatic or heteroaromatic group. Particularly useful R^{13} atoms or groups include a halogen atom, especially fluorine or chlorine and C_{1-6} alkoxy, especially methoxy.

Where R^3 is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl, thiazolidinyl, pyrrolidinonyl, piperidinyl, homopiperidinyl, heptamethyleneiminyl, morpholinyl, piperazinyl or homopiperazinyl group optional substituents include in particular $-(L^5)_p(Alk^5)_qR^{12}$ groups as described earlier.

In one preferred group of compounds of formulae (1), (2a) and (2b) L^1 is present as a $-N(R^8)-$ group. Particularly useful $-N(R^8)-$ groups include $-NH-$, $-N(CH_3)-$, $-N(CH_2CH_3)-$ and $-N(CH_2CH_2CH_3)-$ groups. In this class of compounds n is preferably the integer 1 and Alk^1 is preferably an optionally substituted straight or branched C_{1-6} alkylene chain. Particularly useful Alk^1 chains include $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$ and $-C(CH_3)CH_2-$. R^3 in this group of compounds is preferably a hydrogen atom.

In another preferred group of compounds of formulae (1), (2a) and (2b) Alk^1 is present as an aliphatic-chain as defined herein (i.e. n is the integer 1) and R^3 is a hydrogen atom. In this class of compounds L^1 is preferably

a covalent bond. Compounds of this type where Alk^1R^3 is a C_{1-6} alkyl group, particularly a methyl, ethyl, propyl, butyl, isopropyl, t-butyl or C_{1-6} alkenyl group particularly an allyl group are especially useful. A most especially useful Alk^1R^3 group is a $-\text{C}(\text{CH}_3)_3$ group.

5

In another preferred group of compounds of formulae (1), (2a) and (2b), L^1 is a covalent bond, n is zero and R^3 is an optionally substituted C_{5-7} heterocycloaliphatic group. Especially useful C_{5-7} heterocycloaliphatic groups include optionally substituted piperidinyl, homopiperidinyl, 10 heptamethyleneiminy, pyrrolidinyl, piperazinyl, homopiperazinyl, morpholinyl and thiomorpholinyl groups. Most preferred C_{5-7} heterocycloaliphatic groups are those linked via a ring nitrogen atom to the remainder of the compound of formulae (1), (2a) or (2b). Most especially useful C_{5-7} heterocycloaliphatic groups include optionally substituted 15 pyrrolidin-1-yl, piperidin-1-yl and homopiperidin-1-yl groups. Especially useful optional substituents on these C_{5-7} heterocycloaliphatic groups include optionally substituted C_{1-6} alkyl groups, especially methyl, ethyl and i-propyl groups. Most preferred optionally substituted C_{5-7} heterocycloaliphatic groups include 2-methylpyrrolidin-1-yl, cis and trans 20 2,5-dimethylpyrrolidin-1-yl, 2-methylpiperidin-1-yl, cis and trans 2,6-dimethylpiperidin-1-yl, homopiperidin-1-yl, 2-methylhomopiperidin-1-yl and cis and trans 2,7-dimethylhomopiperidin-1-yl groups.

Particularly useful compounds of the invention include:

- 25 (2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid;
(2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid;
and the salts, solvates, hydrates, N-oxides and carboxylic acid esters,
30 particularly the methyl, ethyl, propyl and i-propyl esters thereof.

Compounds according to the invention are potent and selective inhibitors of α_4 integrins and have advantageous clearance properties, especially those compounds where R is a carboxylic ester or amide. The ability of 35 the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable

additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

- 5 Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

10

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection
15 may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

20

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

25

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichloro-
30 fluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

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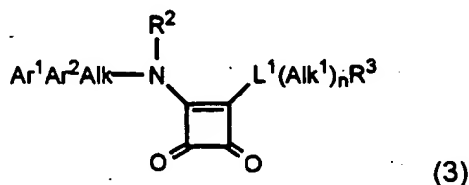
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar¹, Ar², Alk, R¹, R², R³, L¹, L², Alk¹ and n when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991 and the Examples hereinafter]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

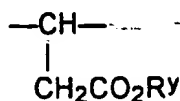
Thus according to a further aspect of the invention, a compound of formula (1) in which R is a -CO₂H group may be obtained by hydrolysis of an ester of formula (3):

29



where Alk represents a group $-\text{CH}_2\text{CH}(\text{CO}_2\text{R}^Y)-$, $-\text{CH}=\text{CH}(\text{CO}_2\text{R}^Y)-$, or

5



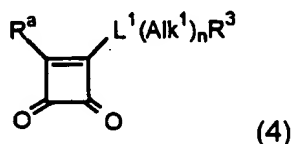
[where R^Y is an alkyl group for example a C_{1-6} alkyl group]

10

The hydrolysis may be performed using either an acid or a base depending on the nature of R^Y , for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium, sodium or potassium hydroxide optionally in an aqueous organic solvent such as an amide e.g. a substituted amide such as dimethylformamide, an ether e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol e.g. methanol at a temperature from ambient to the reflux temperature. Where desired, mixtures of such solvents may be used.

15

20 According to a further aspect of the invention a compound of formula (3) may be prepared by displacement of a leaving group from a compound of formula (4):



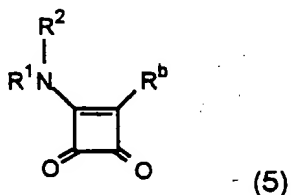
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where R^a is a leaving group, with an amine $\text{R}^1\text{R}^2\text{NH}$ or a salt thereof. Suitable leaving groups represented by R^a include halogen atoms, especially chlorine and bromine atoms, or alkoxy, e.g. methoxy, ethoxy or isopropoxy, aryloxy, e.g. dinitrophenyloxy, or aralkoxy, e.g. benzyloxy, groups.

30

The reaction may be performed in an inert solvent or mixture of solvents, for example a substituted amide such as dimethylformamide, an alcohol such as methanol or ethanol and/or a halogenated hydrocarbon such as dichloromethane, at a temperature from 0°C to the reflux temperature. Where necessary, for example when a salt of an amine R^1R^2NH is used, an organic base such as diisopropylethylamine can be added.

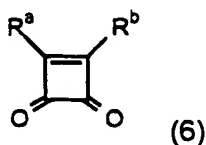
It will be appreciated that the displacement reaction may also be performed on a compound of formula (5):



where R^b is a leaving group as defined for R^a using an intermediate $R^3(Alk^1)_nL^1H$ where $-L^1H$ is a functional group such as an amine ($-NH_2$) using the reaction conditions just described.

Where desired the displacement reaction may also be performed on an intermediate of formulae (4) or (5), R^1R^2NH or $R^3(Alk^2)_nL^1H$ which is linked, for example via its R^1 or R^3 group, to a solid support, such as a polystyrene resin. After the reaction the desired compound of formula (1) may be displaced from the support by any convenient method, depending on the original linkage chosen. Particular examples of such solid phase syntheses are given in the Examples hereinafter.

Intermediates of formulae (4) and (5) are either readily available or may be prepared from an intermediate of formula (6):



where R^a and R^b are as previously defined and an amine R^1R^2NH , $R^3(Alk^1)_nL^1H$ where L^1H is a functional group such as an amine ($-NH_2$) or alcohol ($-OH$), alkyl lithium or aryllithium by displacement as just described for the preparation of compounds of formula (1).

5

Intermediates of formulae R^1R^2NH and $R^3(Alk^1)_nL^1H$ may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions. Particular substitution approaches include conventional
10 alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation and coupling procedures. It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1), (2a), (2b) and (3) where appropriate functional groups exist in these compounds.

15

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example intermediates of formula R^1R^2NH may be obtained from reaction or
20 intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a halogen atom such as bromine or iodine or a sulphonate such as trifluoromethylsulphonate] with a boronic acid $Ar^1B(OH)_2$, optionally in the presence of a base such as a carbonate e.g. sodium or potassium carbonate or an amine e.g. triethylamine or pyridine and a metal complex such as a palladium complex e.g. tetrakis(triphenylphosphine)palladium (0) in a solvent such as
25 an aromatic hydrocarbon e.g. toluene or an ether e.g. 1,2-dimethoxyethane or tetrahydrofuran in the presence of water at an elevated temperature e.g. 80° .

30

In the reaction as just described for the synthesis of intermediates of formula R^1R^2NH boronic acids of formula $Ar^1B(OH)_2$ may be replaced by organometallic reagents such as organostannanes of formula $Ar^1Sn(R^2)_3$ (where R^2 is a C_{1-8} alkyl group), Grignard reagents of formula Ar^1MgHal (where Hal is a halogen atom such as a chlorine, bromine or iodine atom) or organozinc reagents of formula Ar^1ZnHal . In any reaction involving such
35 reagents water is omitted from the reaction conditions as just described,

Intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a sulphonate] may be obtained from intermediates of formula $XAr^2AlkN(R^2)H$ [where X is a hydroxyl (-OH) group] by reaction with an anhydride such as a sulphonic anhydride e.g. trifluoromethanesulphonic anhydride in the presence of a
5 base such as an amine e.g. triethylamine or pyridine in a solvent such as a halogenated hydrocarbon e.g. dichloromethane, at for example 0°C.

In another example, compounds containing a $-L^1H$ or $-L^2H$ group (where L^1 and L^2 is each a linker atom or group) may be treated with an alkylating
10 agent $R^3(Alk^1)_nX^1$ or $R^4L^3(Alk^2)_nX^1$ respectively in which X^1 is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluene-sulphonyloxy group.

15

The reaction may be carried out in the presence of a base such as a carbonate, e.g. cesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, or an organic amine e.g. triethylamine or N,N-diisopropylethylamine or a cyclic amine,
20 such as N-methylmorpholine or pyridine, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

In another example, compounds containing a $-L^1H$ or $-L^2H$ or group as
25 defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X^1 is replaced by a $-C(O)X^2$, $C(S)X^2$, $-N(R^8)COX^2$ or $-N(R^8)C(S)X^2$ group in which X^2 is a leaving atom or group as described for X^1 . The reaction may be performed in the presence of a base, such as a hydride,
30 e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation may be carried out under the same conditions with an acid (for
35 example one of the alkylating agents described above in which X^1 is replaced by a $-CO_2H$ group) in the presence of a condensing agent, for

example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, or a benzotriazole such as [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium]hexafluorophosphate advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction

In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X¹ is replaced by a -S(O)Hal or -SO₂Hal group [in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

In another example, compounds containing a -L¹H or -L²H group as defined above may be coupled with one of the alkylation agents just described but in which X¹ is replaced by an -OH group in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

In a further example, ester groups -CO₂R⁵, -CO₂Alk³ or -CO₂Alk⁷ in the compounds may be converted to the corresponding acid [-CO₂H] by acid- or base-catalysed hydrolysis depending on the nature of the groups R⁵, Alk³ or Alk⁷. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

In a further example, -OR⁵ or -OR¹⁴ groups [where R⁵ or R¹⁴ each represents an alkyl group such as methyl group] in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH₂R¹⁴ group (where R¹⁴ is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [CO₂Alk⁵ or CO₂R⁵] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in the compounds may be converted to a corresponding -OR⁵ or -OR¹⁴ group by coupling with a reagent R⁵OH or R¹⁴OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO₂NHR³] groups in the compounds may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with a sulphonamide R³NHSO₂NH₂ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In another example compounds containing a -NHCSR³ or -CSNHR³ group may be prepared by treating a corresponding compound containing a -NHCOR³ or -CONHR³ group with a thiation reagent, such as Lawesson's Reagent, in an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, at an elevated temperature such as the reflux temperature.

In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

Aromatic halogen substituents in the compounds may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

In another example, sulphur atoms in the compounds, for example when present in a linker group L¹ or L² may be oxidised to the corresponding sulfoxide or sulphone using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

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Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

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Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

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In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

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Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular geometric isomer of the invention.

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The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

- | | | |
|----|-----------------------------------|------------------------------|
| 30 | NMM - N-methylmorpholine; | EtOAc - ethyl acetate; |
| | MeOH - methanol; | BOC - butoxycarbonyl; |
| | DCM - dichloromethane; | AcOH - acetic acid; |
| | DIPEA - diisopropylethylamine; | EtOH - ethanol; |
| | Pyr - pyridine; | Ar - aryl; |
| | DMSO - dimethylsulphoxide; | iPr - isopropyl; |
| 35 | Et ₂ O - diethylether; | Me - methyl; |
| | THF - tetrahydrofuran; | DMF - N,N-dimethylformamid ; |

Fmoc - 9-fluorenylmethoxycarbonyl; DME - 1,2-dimethoxyethane;

aq. - aqueous;

All NMR's were obtained at 300MHz unless otherwise indicated.

5 INTERMEDIATE 1

Methyl (2S)-3-(4-biphenyl)-2-[(2-isopropoxy-3,4-dioxocyclobut-1-enyl)amino]propanoate

A mixture of methyl (2S)-2-amino-3-(4-biphenyl)-propanoate hydrochloride (415mg, 1142mmol), 3,4-diisopropoxy-3-cyclobutene-1,2-dione (281mg, 1.42mmol), DIPEA (247 μ l, 1.42mmol) and MeOH (10ml) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO₂; DCM/MeOH, 98:2) to give the title compound (358mg). δ H (DMSO-d₆, 390K) 8.50 (1H, d, \downarrow 8.0Hz), 7.63-7.56 (4H, m), 7.47-7.42 (2H, m), 7.36-7.32 (3H, m), 5.24-5.18 (1H, m), 4.80-4.75 (1H, m), 3.74 (3H, s), 3.31 (1H, dd, \downarrow 14.2, 5.2Hz), 3.13 (1H, dd, \downarrow 14.2, 9.4Hz), 1.38 (3H, d, \downarrow 6.0Hz), 1.37 (3H, d, \downarrow 6.1Hz); m/z (ES⁺, 70V) 394 (MH⁺).

INTERMEDIATE 2

20 Methyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(4- {[trifluoromethylsulphonyl]oxy}phenyl)propanoate

Triflic anhydride (5.05ml, 30mmol) was added to a mixture of N-BOC tyrosine methyl ester (7.38g, 25mmol) and pyridine (10ml, 125mmol) in DCM (40ml) at 0°. After 45min at 0° water (80ml) and DCM (100ml) were added. The organic phase was washed with NaOH aq. (0.5M, 60ml), water (60ml), citric acid (10%, 2 x 80ml) and water (60ml), dried (Na₂SO₄) and concentrated *in vacuo* to give the title compound as a yellow oil which solidified on standing (10.6g). δ H (CDCl₃) 7.26-7.18 (4H, m), 5.05 (1H, v br d), 4.59 (1H, v br q), 3.70 (3H, s), 3.16 (1H, dd, \downarrow 13.7, 5.7Hz), 3.02 (1H, dd, \downarrow 13.8, 6.5Hz), 1.40 (9H, s); m/z (ES⁺, 70V) 450 (M⁺ + Na).

INTERMEDIATE 3

Methyl (2S)-2-[(*tert*-butoxycarbonyl)amino]-3-(4-[2',6'-dimethoxy]biphenyl)propanoate

35 A mixture of the Intermediate 2 (4.27g, 10mmol), 2,6-dimethoxybenzene boronic acid (4.55g, 25mmol), potassium carbonate (6.9g, 50mmol)

tetrakis(triphenylphosphine)palladium(0) (2.31g) in DME (45ml) and water (5ml) was heated at 80° overnight. The mixture was diluted with EtOAc, washed with dilute HCl, NaHCO₃ (aq.), water and brine, dried (Na₂SO₄) and concentrated *in vacuo*. Column chromatography (SiO₂; EtOAc/hexane, 20:80 - 30:70) gave the title compound (2.27g). δ H (DMSO-d₆) 7.33 (1H, d, \downarrow 8.2Hz), 7.27 (1H, t, \downarrow 8.3Hz), 7.20 (2H, d, \downarrow 8.1Hz), 7.10 (2H, d, \downarrow 8.0Hz), 6.71 (2H, d, \downarrow 8.4Hz), 4.2 (1H, m), 3.63 (9H, s), 3.01 (1H, dd, \downarrow 13.9, 4.5Hz), 2.84 (1H, dd, \downarrow 13.7, 10.3Hz), 1.34 (9H, s); m/z (ES⁺, 70V) 438 (M^+ + Na).

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INTERMEDIATE 4

Methyl (2S)-2-amino-3-(4-[2',6'-dimethoxy]biphenyl)propanoate hydrochloride

Anhydrous HCl was bubbled through a solution of Intermediate 3 (1.30g, 3.13mmol) in EtOAc (30ml) for a few seconds. The mixture was stirred at room temperature for 1h. Some solvent was removed *in vacuo* until material began to precipitate. The precipitate was filtered off and dried to give the title compound as pale yellow crystals (888mg, 81%). δ H (DMSO-d₆) 8.7 (2H, br s), 7.28 (1H, t, \downarrow 8.4Hz), 7.21 (2H, d, \downarrow 8.4Hz), 7.17 (2H, d, \downarrow 8.3Hz), 6.73 (2H, d, \downarrow 8.4Hz), 4.30 (1H, t, \downarrow 6.6Hz), 3.69 (3H, s), 3.64 (6H, s), 3.18 (1H, dd, \downarrow 14.1, 6.2Hz), 3.10 (1H, dd, \downarrow 14.1, 7.1Hz); m/z (ES⁺, 70V) 316 (M^+).

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INTERMEDIATE 5

Methyl (2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-[(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)amino]propanoate

A mixture of Intermediate 4 (325mg, 1.0mmol) 3,4-diisopropoxy-3-cyclobutene-1,2-dione (208mg, 1.05mmol), NMM (115 μ l, 1.05mmol) and MeOH (10ml) was heated at reflux overnight. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with dilute HCl, dried (Na₂SO₄) and concentrated *in vacuo*. Column chromatography (SiO₂; MeOH/DCM, 3:97) gave the title compound as a yellow gum (425mg). δ H (DMSO-d₆, 390K), 8.50 (1H, br d, \downarrow 8.5Hz), 7.26 (1H, t, \downarrow 8.3Hz), 7.22 (2H, d, \downarrow 8.3Hz), 7.16 (2H, d, \downarrow 8.4Hz), 6.73 (2H, d, \downarrow 8.3Hz), 5.22 (1H, sept, \downarrow 6.2Hz), 4.81-4.75 (1H, br m), 3.74 (3H, s), 3.65 (6H, s), 3.29 (1H, dd, \downarrow

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14.2, 5.1Hz), 3.10 (1H, dd, \downarrow 14.2, 9.6Hz), 1.39 (3H, d, \downarrow 6.3Hz), 1.38 (3H, d, \downarrow 6.2Hz); m/z (ES⁺, 70V) 454 (MH⁺).

INTERMEDIATE 6

5 Methyl (2S)-2-[(tert-butoxycarbonyl)amino]-3-(4-[2'-methoxy]biphenyl)propanoate

The title compound (944mg) was prepared from Intermediate 2 (2.14g, 5mmol) and 2-methoxybenzeneboronic acid (1.52g, 10mmol) by a similar method to that used to prepare Intermediate 3. δ H (DMSO-d⁶) 7.67-7.23
10 (6H, m), 7.10-6.97 (3H, m), 4.20 (1H, m), 3.74 (3H, s), 3.63 (3H, s), 3.02 (1H, dd, \downarrow 13.7, 4.9Hz), 2.85 (1H, dd, \downarrow 14.0, 10.2Hz), 1.33 (9H, s); m/z (ES⁺, 70V) 408 (M⁺ + Na).

INTERMEDIATE 7

15 Methyl (2S)-2-amino-3-(4-[2'-methoxy]biphenyl)propanoate hydrochloride

The title compound was obtained from Intermediate 6 by the method used to prepare Intermediate 4. δ H (DMSO-d⁶) 8.68 (2H, br s), 7.44 (2H, d, \downarrow 8.2Hz), 7.36-7.24 (2H, m), 7.26 (2H, d, \downarrow 8.4Hz), 7.10 (1H, d, \downarrow 7.6Hz),
20 7.02 (1H, dt, \downarrow 7.4, 1.0Hz), 4.30 (1H, t, \downarrow 6.5Hz), 3.75 (3H, s), 3.71 (3H, s), 3.23-3.10 (2H, m); m/z (ES⁺, 70V) 286 (MH⁺).

INTERMEDIATE 8

25 Methyl (2S)-3-(4-[2'-methoxy]biphenyl)-2-[(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)amino]propanoate

The title compound was obtained from Intermediate 7 by the method used to prepare Intermediate 5. δ H (DMSO-d⁶, 390K) 8.48 (1H, br d, \downarrow 8.6Hz), 7.41 (2H, d, \downarrow 8.3Hz), 7.34-7.25 (4H, m), 7.10 (1H, dd, \downarrow 8.3, 1.0Hz), 7.02 (1H, dt, \downarrow 7.4, 1.1Hz), 5.21 (1H, sept, \downarrow 6.2Hz), 4.80-4.75 (1H, m), 3.76
30 (3H, s), 3.75 (3H, s), 3.31 (1H, dd, \downarrow 14.2, 5.1Hz), 3.12 (1H, dd, \downarrow 14.3, 9.5Hz), 1.39 (3H, d, \downarrow 6.2Hz), 1.38 (3H, d, \downarrow 6.1Hz); m/z (ES⁺, 70V) 424 (MH⁺).

INTERMEDIATE 9

35 3-(Diethylamino)-4-isopropoxy-3-cyclobutene-1,2-dione

A mixture of 3,4-diisopropoxy-3-cyclobutene-1,2-dione (1.0g, 5.05mmol) and diethylamine (549 μ l, 5.30mmol) in EtOH (25ml) was stirred overnight at room temperature. The solvent was removed *in vacuo* to give the title compound as a yellow oil (1.0g). δ H (DMSO- d_6 , 390K) 5.33-5.27 (1H, m), 3.58 (4H, q, \downarrow 7.1Hz), 1.42 (6H, d, \downarrow 6.1Hz), 1.23 (6H, t, \downarrow 7.2Hz); m/z (ES $^+$, 70V) 212 (MH $^+$).

INTERMEDIATE 10

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-hydroxyphenyl)propionate

Methyl 3-[(amino)(4-hydroxyphenyl)]propionate [Davies S. G. and Ichihara, O. Tet. Asym 2, 3, 183-186 (1991)] (870mg, 4.5mmol) was dissolved in dioxan (5ml) and aqueous sodium hydrogen carbonate solution (5ml). di-tert-butylcarbonate (877mg) in dioxan (2ml) was added and the reaction stirred at room temperature for 16h. Water was added and the solution extracted into EtOAc (x 3), dried over Na $_2$ SO $_4$, filtered and concentrated to give the crude product. Column chromatography (silica; DCM/MeOH 20:1) gave the title compound (900mg, 68%) as a white solid. δ H (DMSO- d_6 , 300K) 9.27 (1H, s), 7.09 (2H, d, \downarrow 8.5Hz), 6.68 (2H, d, \downarrow 8.5Hz), 4.82 (1H, m), 3.54 (3H, s), 2.70 (1H, dd, \downarrow 15.2, 8.7Hz), 2.61 (1H, dd, \downarrow 15.2, 6.5Hz) and 1.35 (9H, s); m/z (ES $^+$, 70V) 318 (M+Na).

INTERMEDIATE 11

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-trifluoromethylsulphonyloxyphenyl)propionate

Intermediate 10 (450mg, 1.53mmol) in DCM (5ml) and pyridine (0.62ml) was cooled to 0 $^\circ$ and trifluoromethylsulphonylanhydride (0.24ml) added. The solution was stirred at 0 $^\circ$ for 30min then quenched with saturated NaHCO $_3$ solution, washed with water, dried over Na $_2$ SO $_4$, filtered and concentrated to give the title compound (430mg, 66%) as a colourless oil. δ H (DMSO- d_6 , 400MHz), 7.40-7.20 (4H, m), 4.98 (1H, br m), 3.56 (3H, s), 2.85 (2H, m) and 1.35 (9H, s). m/z (ES $^+$, 70V) 450 (M+Na).

INTERMEDIATE 12

Methyl (R)-3-[(tert-butoxycarbonyl)amino]-3-(4-[2',6'-dimethoxy]biphenyl)propionate

Intermediate 11 (430mg, 1mmol) was dissolved in DMF (3ml) and triethylamine (0.28ml), 2,6-dimethoxybenzeneboronic acid (367mg), tetrakis(triphenylphosphine) palladium (O) (146mg) added and the mixture heated at 120° for 1h. The mixture was cooled, concentrated, dissolved into EtOAc, wash with water (x 3), brine, dried (Na₂SO₄), filtered and concentrated. Column chromatography (SiO₂; DCM/MeOH 50:1) gave the title compound (270mg, 63%) as a pale brown solid. δ H (DMSO-d₆) 7.30 (5H, m), 6.65 (2H, d, \downarrow 8.4Hz), 5.30 (1H, br m), 5.18 (1H, br m), 3.72 (6H, s), 3.66 (3H, s), 2.89 (2H, m), 1.44 (9H, s); m/z (ES⁺, 70V) 438 (M+Na).

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INTERMEDIATE 13

Methyl (R)-3-amino-3-(4-[2',6'-dimethoxy]biphenyl)propionate

Intermediate 12 (270mg) in EtOAc (5ml) was treated with excess HCl gas then stirred for 30min. The precipitate was filtered to give the title compound (211mg, 95%) as a pale brown solid. δ H (DMSO-d₆) 8.73 (2H, br m), 7.50 (2H, d, \downarrow 8.2Hz), 7.30 (1H, t, \downarrow 8.4Hz), 7.25 (2H, d, \downarrow 8.2Hz), 6.74 (2H, d, \downarrow 8.4Hz), 4.60 (1H, t, \downarrow 7.8Hz), 3.65 (6H, s), 3.60 (3H, s), 3.23 (1H, dd, \downarrow 16.5, 6.3Hz) and 3.04 (1H, dd, \downarrow 16.5, 8.1Hz); m/z (ES⁺, 70V) 299 (M-NH₃).

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INTERMEDIATE 14

Derivatised Resin (1)

Resin bound (S)-3-(4-iodophenyl)-2-(2-([propylamino]-3,4-dioxocyclobut-1-enylamino)propanoic acid (1)

Wang resin (Advanced ChemTech, 5.0g, 0.70mmol/g, 3.50mmol equivalent) in a mixture of DMF (20ml) and DCM (20ml) was treated with N- α -Fmoc-4-iodo-L-phenylalanine (4.51g, 8.75mmol), 1,3-diisopropylcarbodiimide (1.40ml, 8.75mmol) and 4-N,N-dimethylaminopyridine (0.43g, 0.35mmol) and the mixture was agitated at room temperature for 16h. The resin was filtered and washed with DMF, DCM and MeOH, then air-dried. The resin was treated with a 20% solution of acetic anhydride in DMF for 30mins at room temperature, then filtered and washed as before. The resulting resin was treated with a 20% solution of piperidine in DMF (50ml) for 30mins at room temperature, then filtered and washed with DMF, DCM and MeOH. The resin was re-suspended in DMF (50ml) and was treated with 3,4-dimethoxy-3-cyclobut-1,2-dione (2.50g, 17.50mmol) and the

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mixture agitated at room temperature for 16h. The resin was filtered and washed with DMF, DCM and MeOH, then re-suspended in a mixture of DCM (200ml) and MeOH (50ml) and treated with 1-propylamine (2.90ml, 35.00mmol). The reaction mixture was agitated at room temperature for 4h. The resin was filtered and washed with DMF, DCM and MeOH, then air-dried to give the title derivatised resin (1).

EXAMPLE 1

Methyl (2S)-3-(4-biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate
n-Propylamine (104 μ l, 1.26mmol) was added to a solution of Intermediate 1 (412mg, 1.05mmol) in MeOH (10ml). The mixture was stirred at room temperature overnight then the solvent removed *in vacuo*. The residue was dissolved in DCM (100ml), washed with HCl (aqueous) (1M, 30ml), dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a yellow solid (337mg). δ H (DMSO-d₆, 390K) 7.69 (1H, br), 7.65-7.59 (4H, m), 7.55 (1H, br), 7.47-7.44 (2H, m), 7.37-7.33 (1H, m), 7.26 (2H, d, \downarrow 7.5Hz), 5.06 (1H, br), 3.73 (3H, s), 3.45 (2H, br), 3.24 (1H, br), 3.73 (3H, s), 3.45 (2H, br), 3.24 (1H, dd, \downarrow 14.2, 5.2Hz), 3.12 (1H, dd, \downarrow 13.8, 7.7Hz), 1.55-1.48 (2H, m), 0.87 (3H, t, \downarrow 7.3Hz).

EXAMPLE 2

(2S)-3-(4-Biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid
Lithium hydroxide monohydrate (1.03mmol, 43mg) was added to the compound of Example 1 (337mg, 0.86mmol) in THF (10ml) and water (10ml). The mixture was stirred at room temperature overnight. The THF was removed *in vacuo* and the aqueous residue acidified to pH1-2 with HCl (1M). The precipitate was filtered off, washed with water and ether and dried to give the title compound as a brown solid (191mg). δ H (DMSO-d₆, 390K) 7.64-7.59 (2H, m), 7.55-7.52 (2H, m), 7.47-7.46 (2H, m), 7.45-7.31 (3H, m), 7.50-7.20 (2H, br), 5.13-5.11 (1H, br), 3.54-3.46 (2H, m), 3.32 (1H, dd, \downarrow 14.0, 5.3Hz), 3.18 (1H, dd, \downarrow 14.0, 7.1Hz), 1.59-1.53 (2H, m), 0.92 (3H, t, \downarrow 7.4Hz); m/z (ES⁺, 70V) 379 (MH⁺).

EXAMPLE 3

Methyl (2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate

The title compound (327mg, 78%) was prepared from Intermediate 5 (420g, 0.93mmol) by the method used to prepared the compound of Example 1. δ H (DMSO- d_6 , 390K), 7.27 (1H, t, \downarrow 8.3Hz), 7.18 (4H, s), 6.74 (2H, d, \downarrow 8.3Hz), 7.35-7.10 (2H, br), 5.08 (1H, m), 3.73 (3H, s), 3.65 (6H, s), 3.49-3.47 (2H, m), 3.24 (1H, dd, \downarrow 14.2, 5.9Hz), 3.14 (1H, dd, \downarrow 14.2, 7.8Hz), 1.63-1.55 (2H, m), 0.93 (3H, t, \downarrow 7.4Hz); m/z (ES $^+$, 70V) 453 (MH $^+$).

EXAMPLE 4

(2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid

The title compound was prepared from the compound of Example 3 by a similar method to that used to prepare the compound of Example 2. δ H (DMSO- d_6 , 390K) 7.26 (1H, t, \downarrow 8.3Hz), 7.21 (2H, d, \downarrow 8.3Hz), 7.16 (2H, d, \downarrow 8.4Hz), 6.74 (2H, d, \downarrow 8.3Hz), 7.35-7.20 (2H, br), 4.99 (1H, br m), 3.65 (6H, s), 3.51-3.47 (2H, m), 3.26 (1H, dd, \downarrow 14.2, 5.6Hz), 3.11 (1H, dd, \downarrow 14.2, 7.5Hz), 1.63-1.54 (2H, m), 0.93 (3H, t, \downarrow 7.4Hz); m/z (ES $^+$, 70V) 439 (MH $^+$).

EXAMPLE 5

Methyl (2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate

Diethylamine (84 μ l, 0.82mmol) was added to a solution of Intermediate 5 (185mg, 0.408mmol) in MeOH (5ml). The mixture was heated at 50 $^\circ$ for 3h. The solvent was removed *in vacuo*. The residue was purified by column chromatography (SiO $_2$;MeOH/DCM, 2:98) to give the title compound as a colourless gum (164mg, 86%). δ H (DMSO- d_6) 7.77 (1H, d, \downarrow 8.9Hz), 7.26 (1H, t, \downarrow 8.3Hz), 7.22 (2H, d, \downarrow 8.3Hz), 7.10 (2H, d, \downarrow 8.2Hz), 6.70 (2H, d, \downarrow 8.4Hz), 5.23-5.15 (1H, m), 3.71 (3H, s), 3.61 (6H, s), 3.51 (4H, br m), 3.30-3.20 (CH $_2$ Ar, under HOD signal), 3.06 (1H, dd, \downarrow 13.9, 10.9Hz), 1.08 (6H, t, \downarrow 7.1Hz); m/z (ES $^+$, 70V) 467 (MH $^+$).

EXAMPLE 6

(2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid

The title compound was prepared from the compound of Example 5 by a similar method to that used to prepare the compound of Example 2.

- 5 (DMSO-d₆, 390K) 7.39-7.30 (3H, m), 7.22 (2H, d, \downarrow 8.3Hz), 7.01 (1H, br d, \downarrow 7.3Hz), 6.79 (2H, d, \downarrow 8.0Hz), 5.27-5.23 (1H, m), 3.70 (6H, s), 3.68-3.52 (3H, m), 3.38 (1H, dd, \downarrow 14.3, 5.1Hz), 3.21 (1H, dd, \downarrow 14.2, 9.1Hz), 1.22 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 453 (MH⁺).

10 **EXAMPLE 7**

Methyl (2S)-3-(4-[2'-methoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate

The title compound was obtained from intermediate 8 by the method used to prepare the compound of Example 5.

- 15 δ H (DMSO-d₆) 7.77 (1H, d, \downarrow 9.0Hz), 7.37 (2H, d, \downarrow 8.2Hz), 7.34-7.21 (2H, m), 7.27 (2H, d, \downarrow 8.1Hz), 7.08 (1H, d, \downarrow 7.6Hz), 6.99 (1H, t, \downarrow 7.4Hz), 5.18 (1H, m), 3.72 (3H, s), 3.71 (3H, s), 3.50 (4H), ~3.30 (1H), 3.07 (1H, dd, \downarrow 13.9, 10.8Hz), 1.07 (6H, t, \downarrow 7.1Hz), m/z (ES⁺, 70V) 437 (MH⁺).

20 **EXAMPLE 8**

(2S)-3-(4-[2'-Methoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid

The title compound was obtained from the compound of Example 7 by the method used to prepare the compound of Example 2.

- 25 δ H (DMSO-d₆, 390K) 7.40 (2H, d, \downarrow 8.4Hz), 7.33-7.25 (2H, m), 7.30 (2H, d, \downarrow 8.3Hz), 7.09 (1H, dd, \downarrow 8.2, 1.0Hz), 7.02 (1H, dt, \downarrow 7.4, 1.1Hz), 6.95 (1H, br d), 5.21-5.17 (1H, m), 3.75 (3H, s), 3.58-3.52 (4H, m), 3.32 (1H, dd, \downarrow 14.2, 5.2Hz), 3.17 (1H, dd, \downarrow 14.2, 9.2Hz), 1.16 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 423 (MH⁺).

30

EXAMPLE 9

Methyl (2S)-3-(4-[2'-methoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate

The title compound was obtained from Intermediate 8 by the method used to prepare the compound of Example 3.

- 35 δ H (DMSO-d₆, 390K) 7.42 (2H, d, \downarrow 8.3Hz), 7.34-7.24 (2H, m), 7.30 (2H, br), 7.23 (2H, d, \downarrow 8.2Hz), 7.10

(1H, dd, \downarrow 8.2, 0.9Hz), 7.02 (1H, dt, \downarrow 7.4, 1.1Hz), 5.08 (1H, t, \downarrow 6.7Hz), 3.76 (3H, s), 3.74 (3H, s), 3.49 (2H, t, \downarrow 6.8Hz), 3.26 (1H, dd, \downarrow 14.1, 5.8Hz), 3.14 (1H, dd, \downarrow 14.1, 7.7Hz), 1.59 (2H, sext, \downarrow 7.1Hz), 0.93 (3H, t, \downarrow 7.4Hz), m/z (ES⁺, 70V) 423 (MH⁺).

5

EXAMPLE 10**(2S)-3-(4-[2'-Methoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid**

The title compound was obtained from the compound of Example 9 by the method used to prepare the compound of Example 2. δ H (DMSO-d₆, 390K) 7.41 (2H, d, \downarrow 8.3Hz), 7.34-7.23 (6H, m, ArH), 7.10 (1H, dd, \downarrow 8.2, 1.0Hz), 7.02 (1H, dt, \downarrow 7.4, 1.1Hz), 5.01-4.98 (1H, m), 3.76 (3H, s), 3.49 (1H, br t, \downarrow 6.7Hz), 3.27 (1H, dd, \downarrow 14.2, 5.6Hz), 3.13 (1H, dd, \downarrow 14.2, 7.5Hz), 1.58 (2H, sext, \downarrow 7.2Hz), 0.93 (3H, t, \downarrow 7.4Hz); m/z (ES⁺, 70V) 409 (MH⁺).

15

EXAMPLE 11**Methyl (2S)-3-(4-biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoate**

A mixture of (2S)-2-amino-3-[4-biphenyl]propanoate hydrochloride (437mg, 1.5mmol), Intermediate 9 (275mg, 1.5mmol) and DIPEA (261 μ l, 1.5mmol) in MeOH (10ml) was stirred at room temperature overnight. The solvent was removed *in vacuo*. The residue was dissolved in DCM, washed with dilute HCl, dried (Na₂SO₄) and concentrated *in vacuo*. Crystallisation (EtOAc) gave the title compound as yellow crystals (308mg). δ H (DMSO-d₆, 390K) 7.61-7.58 (2H, m), 7.56-7.44 (2H, m), 7.42-7.40 (2H, m), 7.35-7.30 (3H, m), 7.10 (1H, d, \downarrow 8.7Hz), 5.29-5.24 (1H, m), 3.73 (3H, s), 3.57-3.56 (4H, m), 3.32 (1H, dd, \downarrow 14.2, 5.4Hz), 3.17 (1H, dd, \downarrow 14.2, 9.2Hz), 1.14 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 407 (MH⁺).

25

30

EXAMPLE 12**(2S)-3-(4-Biphenyl)-2-((2-[diethylamino]-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid**

The title compound was obtained from the compound of Example 11 by the method used to prepare the compound of Example 2. δ H (DMSO-d₆, 390K) 7.52-7.49 (2H, m), 7.46-7.43 (2H, m), 7.35-7.31 (2H, m), 7.27-7.21

35

(3H, m), 5.10-5.07 (1H, m), 3.47-3.39 (4H, m), 3.22 (1H, dd, \downarrow 14.2, 5.2Hz), 3.07 (1H, dd, \downarrow 14.2, 9.1Hz), 1.05 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 393 (MH⁺).

5 **EXAMPLE 13**

Methyl (R)-3-[4-(2',6'-dimethoxy)biphenyl]-3-[2-isopropoxy-3,4-dioxo-cyclobut-1-enyl]amino]propionate

Intermediate 13 (211mg, 0.6mmol) in MeOH (3ml) was treated with DIPEA (0.23ml) and 3,4-diisopropoxy-3-cyclobutene-1,2-dione (130mg) at
10 room temperature for 16h. The mixture was concentrated then purified by column chromatography (silica; DCM/MeOH 50:1) gave the title compound (196mg, 72%) as a pale yellow oil. δ H (DMSO-d₆) 9.34 (1H, m), 7.29 (3H, m), 7.19 (2H, d, \downarrow 7.9Hz), 6.71 (2H, d, \downarrow 8.4Hz), 5.74 (1H, m), 5.24 (1H, m), 3.64 (6H, m), 3.92 (3H, s), 3.0 (2H, m), 1.35 (6H, m). m/z (ES⁺, 70V)
15 454 (MH⁺).

EXAMPLE 14

Methyl (R)-3-[2-(diethylamino)-3,4-dioxo-cyclobut-1-enyl]-3-[4-(2',6'-dimethoxy)biphenyl] propionate

20 The compound of Example 13 (190mg, 0.42mmol) in MeOH (4ml) was treated with diethylamine (0.065ml) and stirred at room temperature for 1h. The precipitate was filtered and dried to give the title compound (169mg, 87%) as a white solid. δ H (DMSO-d₆) 7.37 (2H, d, \downarrow 8.2Hz), 7.28 (1H, t, \downarrow 8.3Hz), 7.18 (2H, d, \downarrow 8.2Hz), 6.71 (2H, d, \downarrow 8.3Hz), 5.90 (1H, m), 3.64
25 (3H, s), 3.60 (3H, s), 3.50 (4H, m), 3.30 (3H, s), 3.00 (2H, m) and 1.23 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 467 (MH⁺).

EXAMPLE 15

(R)-3-[2-(Diethylamino)-3,4-dioxo-cyclobut-1-enyl]amino-3-[4-(2',6'-dimethoxy)biphenyl]propionic acid

30 The compound of Example 14 in THF (2ml) and H₂O (2ml) was treated with lithium hydroxide (22mg) and stirred at room temperature for 2h. The THF was removed *in vacuo* and the remaining solution acidified with dilute HCl solution to give a white precipitate which was filtered and dried to give
35 the title compound (99mg, 63%). δ H (DMSO-d₆, 400K) 7.42 (2h, d, \downarrow 8.1Hz), 7.25 (3H, m), 6.75 (2H, d, \downarrow 8.1Hz), 5.92 (1H, m), 3.68 (6H, s),

3.60 (2H, q, \downarrow 7.1Hz), 3.58 (2H, q, \downarrow 7.1Hz), 3.04 (1H, dd, \downarrow 15.7, 8.3Hz), 2.95 (1H, dd, \downarrow 15.7, 5.9Hz) and 1.21 (6H, t, \downarrow 7.1Hz); m/z (ES⁺, 70V) 453 (MH⁺).

5 **EXAMPLE 16**

(2S)-3-(4-Biphenyl)-2-[(2-morpholino-3,4-dioxocyclobut-1-enyl)amino] propanoic acid

N- α -Fmoc-L-4-biphenylalanine Wang resin (Advanced ChemTech, 200mg, 0.50mmol/g, 0.1mmol equivalent) was treated with a 20% solution
10 of piperidine in DMF (2ml) for 30min at room temperature, then filtered and washed with DCM. The resin was re-suspended in DMF (2ml) and treated with 3,4-dimethoxy-3-cyclobutene-1,2-dione (99mg, 0.7mmol). The resulting mixture was heated at 70° for 18h. The resin was filtered and washed with DCM then re-suspended in a mixture of DCM (0.4ml) and
15 ethanol (1.6ml) and treated with morpholine (87mg, 1.0mmol). The resin was agitated at room temperature for 18h then filtered and washed with DCM. The resin was treated with a solution of trifluoroacetic acid/DCM (95:5, 2ml) for 3h, then filtered. The filtrate was evaporated to afford the crude product which was purified by preparative HPLC to afford the title
20 compound (4mg).

HPLC-MS Retention time 2.44min 407 (MH⁺).

EXAMPLE 17

(2S)-3-[4-(4'-Methoxy)biphenyl]-2-[(2-(propylamino)3,4-dioxocyclobut-1-enyl)amino]propanoic acid

A slurry of derivatised resin (1) (200mg) in anhydrous, degassed DMF (2ml) was treated with 4-methylbenzeneboronic acid (49mg, 0.35mmol), triethylamine (0.1ml, 0.67mmol) and tetrakis(triphenyl)phosphine palladium (0) (20mg, 0.17mmol). The resulting mixture was agitated at 100° for 2h
30 then cooled to room temperature. The resin was filtered and washed with 0.5% (w/w) sodium diethyldithiocarbamate solution in DMF, 0.5% (w/w) DIPEA solution in DMF, DMF, DCM and MeOH then air-dried. The resin was treated with a solution of trifluoroacetic acid/DMF (95:5, 1ml) for 1h, then filtered. The filtrate was evaporated to afford the title compound
35 (1mg).

HPLC-MS Retention time 2.62min 393 (MH⁺).

LC-MS Conditions : Luna C18(2) 50 x 2.0mm (3um) column, running a gradient of 95% [0.1% aqueous formic acid], 5% [0.1% formic acid in acetonitrile] to 10% [0.1% aqueous formic acid], 90% [0.1% formic acid in acetonitrile] over 2min, then maintaining the mobile phase at that ratio for a further 1min. Flow rate 0.8ml/min. MS was acquired by API electrospray in positive ion mode, at 70V, scanning from 120 to 750amu.

The compounds of Examples 18 to 23 were prepared from derivatised resin (1) in a similar manner to the compound of Example 17, using the arylboronic acid shown.

EXAMPLE 18

(2S)-3-[4-(2'-(Trifluoromethyl)biphenyl)]-2-((2-(1-propylamino)-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid
2-(Trifluoromethyl)benzeneboronic acid gave the title compound (1mg)
HPLC-MS Retention time 2.62min 447 (MH⁺).

EXAMPLE 19

(sS)-3-[4-(2'-Formyl)biphenyl]-2-((2-(1-propylamino)-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid
2-Formylbenzeneboronic acid gave the title compound (2mg)
HPLC-MS Retention time 2.45min 407 (MH⁺).

EXAMPLE 20

(2S)-3-[4-(2',5'-Dimethoxy)biphenyl]-2-((2-(1-propylamino)-3,4-dioxocyclobut-1-enyl)amino)propanoic acid
2,5-Dimethoxybenzeneboronic acid gave the title compound (2mg)
HPLC-MS Retention time 2.53min 439 (MH⁺).

EXAMPLE 21

(2S)-3-[4-(2'-Formyl-5'-methoxy)biphenyl]-2-((2-(1-propylamino)-3,4-dioxocyclobut-1-enyl)amino)propanoic acid
2-Formyl-5-methoxybenzeneboronic acid gave the title compound (5mg)
HPLC-MS Retention time 2.46min 437 (MH⁺).

EXAMPLE 22

(2S)-3-[4-(5'-Chloro-2'-methoxy)biphenyl]-2-((2-(1-propylamino)-3,4-dioxo-cyclobut-1-enyl)amino)propanoic acid

5-Chloro-2-methoxybenzeneboronic acid gave the title compound (3mg)

- 5 HPLC-MS Retention time 2.64min 443 (MH⁺).

EXAMPLE 23

(2S)-3-[4-(5'-Formyl-2'-methoxy)biphenyl]-2-((2-(1-propylamino)-3,4-dioxocyclobut-1-enyl)amino)propanoic acid

- 10 5-Formyl-2-methoxybenzeneboronic acid gave the title compound (5mg)

HPLC-MS Retention time 2.42min 437 (MH⁺).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

20

α₄β₁ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

- 96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fcγ-specific antibody [Jackson Immuno Research 109-006-098: 100 μl at 2 μg/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μl containing 2.5 x 10⁵ Jurkat cells in the presence or absence of titrated test compounds.

- Each plate was washed (2x) with medium and the adherent cells were fixed with 100μl methanol for 10 minutes followed by another wash. 100μl 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100μl 50% (v/v)

ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

- 5 This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lymphoblastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

10

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

- 96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 15 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5x 10⁵ K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed 20 and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic

- 96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h 25 at 37°C. 2 x 10⁵ freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 30 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ 35 (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

α IIb/ β ₃-dependent human platelet aggregation

- Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6×10^8 /ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl₂·H₂O 0.427; CaCl₂ 0.2; KCl 0.2; D-glucose 1.0; NaHCO₃ 1.0; NaHPO₄·2H₂O 0.065). Aggregation was monitored following addition of 2.5 μ M ADP (Sigma) in the presence or absence of inhibitors.

- In the above assays the preferred compounds of the invention in which R¹ is an α_4 integrin binding group, such as the compounds of the Examples generally have IC₅₀ values in the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ assays of 1 μ M and below. In the other assays featuring α integrins of other subgroups the same compounds had IC₅₀ values of 50 μ M and above thus demonstrating the potency and selectivity of their action against α_4 integrins.

- The advantageous clearance properties of compounds according to the invention may be demonstrated as follows:

- Hepatic clearance, whether metabolic or biliary, can make a substantial contribution to the total plasma clearance of a drug. The total plasma clearance is a principal parameter of the pharmacokinetic properties of a medicine. It has a direct impact on the dose required to achieve effective plasma concentrations and has a major impact on the elimination half-life and therefore the dose-interval. Furthermore, high hepatic clearance is an indicator of high first-pass hepatic clearance after oral administration and therefore low oral bioavailability.

- Many peptidic and non-peptidic carboxylic acids of therapeutic interest are subject to high hepatic clearance from plasma. Except for drugs which function in the liver, hepatic uptake from blood or plasma is undesirable because it leads to high hepatic clearance if the compound is excreted in

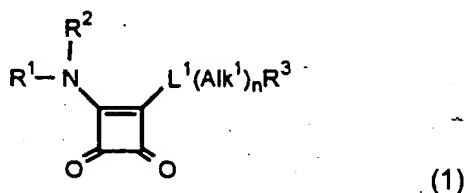
bile or metabolised, or if the substance is not cleared from the liver, it may accumulate in the liver and interfere with the normal function of the liver.

5 The total plasma clearance of a compound according to the invention can be determined as follows:
a small dose of the compound in solution is injected into a vein of a test animal. Blood samples are withdrawn from a blood vessel of the animal at several times after the injection, and the concentration of compound in the bleed or plasma is measured using a suitable assay. The area under the
10 curve (AUC_{iv}) is calculated by non-compartmental methods (for example, the trapezium method) or by pharmacokinetic modelling. The total plasma clearance (CL_p) is calculated by dividing the *intravenous* dose (D_{iv}) by the AUC_{iv} for the blood plasma concentration - time course of a drug administered by the *intravenous* route: $CL_p = D_{iv} \div AUC_{iv}$

15 When tested in this manner, compounds according to the invention are not rapidly or extensively extracted by the liver and have low total plasma clearance where low is defined as less than 10 ml/min/kg in the laboratory rat (Sprague Dawley CD). This compares favourably with functionally
20 equivalent integrin binding compounds in which the square acid framework and/or the carboxylic ester or amide R group of compounds of formula (1) is not present.

CLAIMS

1. A compound of formula (1):

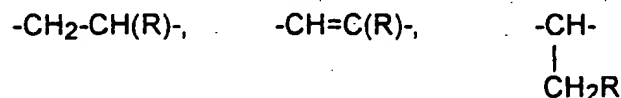


wherein

R¹ is a group Ar¹Ar²Alk- in which:

Ar¹ is an optionally substituted aromatic or heteroaromatic group;

Ar² is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; and Alk is a chain



in which R is a carboxylic acid (-CO₂H) or a derivative or biostere thereof;

R² is a hydrogen atom or a C₁₋₆alkyl group;

L¹ is a covalent bond or a linker atom or group;

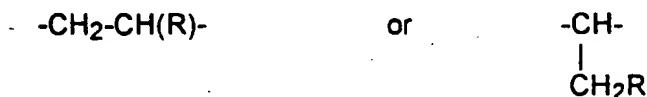
n is zero or the integer 1;

Alk¹ is an optionally substituted aliphatic chain;

R³ is a hydrogen atom or an optionally substituted heteroaliphatic, cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which Alk is a chain

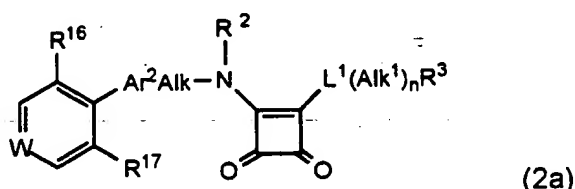


3. A compound according to Claim 1 or Claim 2 in which R is a carboxylic acid (-CO₂H) group.

4. A compound according to Claim 1 or Claim 2 in which R is an esterified carboxyl group of formula $-\text{CO}_2\text{Alk}^7$.
- 5 5. A compound according to any one of Claims 1 to 4 in which Ar^2 is an optionally substituted phenylene group.
6. A compound according to any one of Claims 1 to 5 in which Ar^1 is an optionally substituted phenyl, or five-, six- or ten-membered
10 heteroaromatic group.
7. A compound according to Claim 6 in which Ar^1 is an optionally substituted pyridyl, pyrimidinyl, naphthyridinyl, quinolinyl or isoquinolinyl group.
15
8. A compound according to any one of Claims 1 to 7 in which L^1 is a $-\text{N}(\text{R}^8)-$ group where R^8 is a hydrogen atom or an optionally substituted C_{1-6} alkyl group.
- 20 9. A compound according to Claim 8 in which R^8 is a methyl, ethyl or n-propyl group.
10. A compound according to any one of Claims 1 to 7 in which L^1 is a covalent bond.
25
11. A compound according to any one of Claims 1 to 10 in which n is the integer 1 and Alk^1 is an optionally substituted straight or branched C_{1-6} alkylene chain and R^3 is a hydrogen atom.
- 30 12. A compound according to Claim 11 in which Alk^1 is a $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)\text{CH}_2-$ or $-\text{C}(\text{CH}_3)_2\text{CH}_2-$ chain.
- 35 13. A compound according to any one of Claims 1 to 7 in which L^1 is a covalent bond, n is zero and R^3 is an optionally substituted C_{5-7} heterocycloaliphatic group.

14. A compound according to Claim 13 in which R³ is an optionally substituted piperidinyl, homopiperidinyl, heptamethyleneiminyl, pyrrolidinyl, piperazinyl, homopiperazinyl, morpholinyl or thiomorpholinyl group.

15. A compound according to Claim 1 of formula (2a):



wherein -W= is -CH= or -N=;

R¹⁶ and R¹⁷, which may be the same or different is each a hydrogen atom or an atom or group -L²(Alk²)_tL³(R⁴)_u in which;

L² is a covalent bond or a linker atom or group;

Alk² is an aliphatic or heteroaliphatic chain;

t is zero or the integer 1;

L³ is a covalent bond or a linker atom or group;

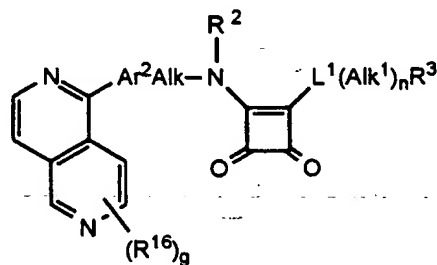
u is the integer 1, 2 or 3;

R⁴ is a hydrogen or halogen atom or a group selected from optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R⁵)- (where R⁵ is a hydrogen atom or an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl group), -C(O)- or -C(S)- groups], -OR⁵ -SR⁵, -NR⁵R⁶ [where R⁶ is as just defined for R⁵ and may be the same or different], -NO₂, -CN, -CO₂R⁵, -SO₃H, -SOR⁵, -SO₂R⁵, -SO₃R⁵, -OCO₂R⁵, -CONR⁵R⁶, -OCONR⁵R⁶, -CSNR⁵R⁶, -COR⁵, -OCOR⁵, -N(R⁵)COR⁶, -N(R⁵)CSR⁶, -SO₂N(R⁵)(R⁶), -N(R⁵)SO₂R⁶, -CON(R⁵)SO₂R⁶, -N(R⁵)CON(R⁶)(R⁷) [where R⁷ is a hydrogen atom or an optionally substituted C₁₋₆alkyl or C₃₋₈cycloalkyl group], -N(R⁵)CSN(R⁶)(R⁷) or -N(R⁵)SO₂N(R⁶)(R⁷), provided that when t is zero and each of L²

and L^3 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom

and the salts, solvates, hydrates and N-oxides thereof.

- 5 16. A compound according to Claim 1 of formula (2b):



(2b)

wherein R^{16} is a hydrogen atom or a group $-L^2(Alk^2)_tL^3(R^4)_u$ in which;

L^2 is a covalent bond or a linker atom or group;

Alk^2 is an aliphatic or heteroaliphatic chain;

t is zero or the integer 1;

L^3 is a covalent bond or a linker atom or group;

u is the integer 1, 2 or 3;

g is the integer 1, 2, 3 or 4;

R^4 is a hydrogen or halogen atom or a group selected from optionally substituted C_{1-6} alkyl or C_{3-8} cycloalkyl, -Het, [where Het is an optionally substituted monocyclic C_{5-7} carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R^5)- (where R^5 is a hydrogen atom or an optionally substituted C_{1-6} alkyl or C_{3-8} cycloalkyl group), -C(O)- or -C(S)- groups], -OR⁵, -SR⁵, -NR⁵R⁶ [where R^6 is as just defined for R^5 and may be the same or different], -NO₂, -CN, -CO₂R⁵, -SO₃H, -SOR⁵, -SO₂R⁵, -SO₃R⁵, -OCO₂R⁵, -CONR⁵R⁶, -OCONR⁵R⁶, -CSNR⁵R⁶, -COR⁵, -OCOR⁵, -N(R^5)COR⁶, -N(R^5)CSR⁶, -SO₂N(R^5)(R^6), -N(R^5)SO₂R⁶, -CON(R^5)SO₂R⁶, -N(R^5)CON(R^6)(R^7) [where R^7 is a hydrogen atom or an optionally substituted C_{1-6} alkyl or C_{3-8} cycloalkyl group], -N(R^5)CSN(R^6)(R^7) or -N(R^5)SO₂N(R^6)(R^7), provided that when t is zero and each of L^2

and L^3 is a covalent bond then u is the integer 1 and R^4 is other than a hydrogen atom
and the salts, solvates, hydrates and N-oxides thereof.

- 5 17. A compound which is:
(2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[1-propylamino]-3,4-dioxo-
cyclobut-1-enyl)amino)propanoic acid;
(2S)-3-(4-[2',6'-dimethoxy]biphenyl)-2-((2-[diethylamino]-3,4-dioxo-
cyclobut-1-enyl)amino)propanoic acid;
10 and the salts, solvates, hydrates, N-oxides and carboxylic acid esters,
particularly the methyl, ethyl, propyl and i-propyl esters thereof.
18. A pharmaceutical composition comprising a compound according to
Claim 1 together with one or more pharmaceutically acceptable
15 carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

Int lional Application No
PCT/GB 00/04995

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C225/20 C07C229/46 C07D295/12 A61K31/13 A61K31/435
A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 18460 A (DUGGAN MARK E ;MERCK & CO INC (US); HARTMAN GEORGE D (US)) 7 May 1998 (1998-05-07) the whole document -----	1

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

14 February 2001

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20/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Paténtisaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Goetz, G

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int l Application No

PCT/GB 00/04995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818460 A	07-05-1998	AU 722360 B	03-08-2000
		AU 5239998 A	22-05-1998
		EP 0946165 A	06-10-1999
		US 5952341 A	14-09-1999